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THE HUMAN PROTEOME PROJECT:

UNLOCKING THE MYSTERIES OF HUMAN LIFE AND UNLEASHING ITS POTENTIAL

by

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BIOGRAPHY

Lieutenant Colonel Andrew B. Meadows is currently a student at the Air War College, Maxwell AFB, Alabama. Colonel Meadows entered the Air Force in 1996 with duty as a clinical pharmacist at the 59th Medical Wing, Lackland AFB, Texas. In 2000, he attended the US Army-Baylor University Graduate Program in Healthcare Administration at Fort Sam Houston, Texas, followed by an assignment as Pharmacy Flight Commander at Hill Air Force Base, Utah. After a year at Air Command and Staff College where he earned Distinguished Graduate honors, he was assigned as Pharmacy Flight Commander at Maxwell AFB, Alabama. In early 2007, Colonel Meadows deployed as the Jordanian Armed Forces Liaison Officer during Operation ENDURING FREEDOM, and upon his return, served as the Air University Commander's Executive Officer supporting the continuum of Air Force education. Prior to his current assignment, Colonel Meadows was Commander, 42d Aeromedical-Dental Squadron , Maxwell AFB, Alabama.

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INTRODUCTION

Imagine a future clandestine operation where a lone government operative checks into the Presidential Suite of a luxury hotel in downtown Paris where three days earlier the Prime Minister of an unfriendly regime also stayed. The agent collects hair from the shower drain, places it in an airtight container before enjoying a nice meal and restful night's sleep. The next day, the hairs arrive back at the lab where DNA sequencing and proteomic data generation follows. A week later, the Prime Minister is shaking hands following a speech in Amsterdam when he encounters an elderly woman seeking to greet him. He recoils slightly at the excessive perfume he notes emanating from her direction. Being a consummate politician, he calmly greets her and moves on. Unknowingly, the Prime Minister just inhaled perfume laced with an opioid-like, performance-degradation agent developed to bind receptors in his brain based on his specific genetic and proteomic make-up. Over the next few days, during the final weapons treaty negotiation meetings, his closest staff members note his increased lethargy, decreased assertiveness and unusual level of agreeableness with the opposing nation's Prime Minister. After signing the new treaty that significantly disadvantaged his nation's security, he regains his normal mental capacity and does not recognize, or at least acknowledge, his recent decreased capacity.

A scenario such as this could happen in the future, possibly as early as the 2030s. While future biological technology has the potential for "evil" as described in the vignette above, the current driver in advancing this research is primarily medical in nature. As with most technologies, new modalities often have the potential for dual use. This fact is especially true in the biological realm as outlined in the saying, "the only difference between medicine and poison

is the dose." In the next several decades, general scientific inquisitiveness and economic factors will advance this field of study improving health and medical treatments for the overall good of humankind. As these advances develop, there will undoubtedly be avenues for malicious application of these findings just as there will be "unknown" outcomes that even today's greatest experts cannot fathom.

Revolutionary biological advances enter the realm of the possible with the fusion of advanced computing technology, findings of the Human Genome Project and results from the less familiar field of proteomics. The Human Genome Project was a revolutionary scientific activity yielding the blueprint of human life. The limited industrialization of this genome technology in 2010 will certainly change over the next several decades, particularly when combined with the results of Human Proteome Project.

The Human Proteome Project is the critical bridge between knowledge of the genome and full operationalization of tactics and techniques to manipulate biological processes in very deliberate and specific ways. These findings will create synergies leading to the specific and precise exploitation of genetic data. The Human Proteome Project will yield such comprehensive knowledge of the biological and molecular function of human life that medical diagnosis and intervention will be radically altered. These effects will apply to all areas of healthcare in general, but the military will employ these agents in support of its unique requirements, such as better trauma care as well as highly effective and precisely targeted performance modification effects.

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THE COMING BIOLOGICAL REVOLUTION

The last several hundred years have seen the industrial, technological and information revolutions emerge as the driving forces in the international community. The coming years will witness the emergence of a biological revolution which will mature faster and have far greater impact on humanity. In the year 2011, only the tip of the biological iceberg has revealed itself. The coming decades will usher in a biological revolution as genomics and related fields mature. This maturation will enable the specific delineation of each gene's control of proteins and other intermediate molecules that keep our bodies functioning normally. The Human Genome Project is the seminal, enabling event to launch this emerging revolution.

Human Genome Project. Often compared to the Manhattan Project for its size, scope, and impact on humanity, the Human Genome Project is arguably the most significant scientific discovery in the last half century. It began in 1993 with a goal of sequencing the complete human genome from 23 pairs of chromosomes. This massive undertaking ended in 2003, approximately two years earlier than planned, at a cost of $3 billion.[1] When fully developed, information obtained from this project will help scientists and the medical profession at large, better understand the natural course of disease, identify patients at risk for diseases with a genetic link, better tailor treatment modalities and accelerate the drug development process.[2] To date, these data have powered the biotechnology industry's pursuit of new therapeutic agents as well as spawned further research to define the specific biological function of every gene.

On a notional continuum where 1 is the basic scientific discovery stage and 10 is a fully developed and mature technology (such as the personal computer), genomic science could be described in the 4 to 5 range. At this point in genomic science's development, there is a solid

understanding of the basic technology, but it has not yet undergone the full industrialization or optimization that will uncover its maximum potential.

Synthetic Biology. This fusion of results from the Human Genome Project and advanced computers yielded the new field of science known as synthetic biology. Synthetic biology is "the design and construction of new biological parts, devices and systems" as well as "the re-design of existing, natural biological systems for useful purposes."[3] Through blending of DNA sequencing information with advanced computing technology, scientists may now digitize data from the four nucleic acids (adenine, thymine, guanine, and cytosine, often depicted as A, T, G and C, respectively) found in an specific organism's DNA and input into machine code consisting of a sequence of 1's and 0's.[4] Examples of this process are already in the works.

As leaders and innovators in synthetic biology, researchers at the J. Craig Venter Institute recently created the world's first, self-replicating synthetic bacterial cell. As in chemistry, where scientists routinely synthesize molecules with a known chemical formula and structure using precursor compounds, the Venter team knew the make-up of a simple bacterium's DNA (*Mycoplasma mycoides*) and attempted to build it synthetically. Starting with bottles containing nothing more than solutions of the four nucleic acids (adenine, thymine, guanine, and cytosine), they eventually combined them in a DNA chain of more than one million base pairs. After inserting the DNA chain into another related, but different, simple bacterial cell (*Mycoplasma capricolum*) with its native DNA removed, the cell was able to replicate as normal. All future generations were fully functional *Mycoplasma mycoides* cells matching the synthetic DNA, no longer exhibiting characteristics of the *Mycoplasma capricolum* cells used as a vehicle.

Descendent cells showed exact replications of the synthetic DNA constructed by Venter's team as evidenced by the presence of particular isotope watermarks for authentication.[5]

Venter's effort represents a seminal work in biology. Essentially, Venter's team of scientists reversed the already known process and started with "1's and 0's in a computer to define the characteristics of a living cell."[6] The ability to build DNA in a laboratory from bottles of reagents controlled by computers under the direction of researchers is a historic step in the making of a biological life form. Future researchers will build upon this work using more complex cell types and also by altering specific genes to modify expressed traits.

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THE REVOLUTION'S NEXT CHAPTER

Despite the remarkable magnitude and significance of the Human Genome Project and the field of synthetic biology, researchers have not yet uncovered the "Rosetta Stone" so highly sought to understand life. As an analogy, the genome represents simply an architectural rendering of a life form, but science still lacks the knowledge to comprehend the myriad interactions and processes manifested in a fully constructed organism. As stated by Cohen et al,

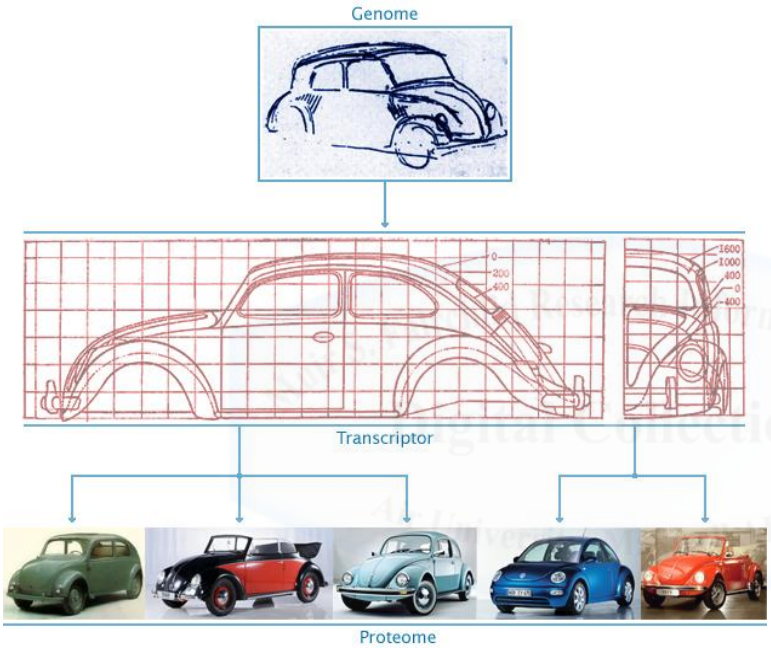
> "[t]he genome is a reservoir of DNA sequence information and a vehicle for transmitting this information; the meaning of DNA emerges from the cellular processing of this raw information into proteins and other functional molecules. The genome is thus akin to a toolbox of DNA sequences that provide molecular tools as requested by the internal state of the organism and the state of the environment."[7]

As further described by the Centre for Genetics Education, "while the number of genes in humans and other organisms is surprisingly similar, humans have an average of three times as many kinds of proteins as the fly or worm. This is because the genetic code of the human genes can be read in a variety of ways, producing on average three proteins per gene compared to one protein per gene in the worm."[8] As this quote describes, genetic knowledge is an important but not sufficient at a level for complete mastery of biological life.

Proteomics. Scientists involved with the Human Genome Project acknowledged the need for follow on investigation and identified three challenges that require additional study to unlock the full potential of the genetic code. All of these future challenges are interrelated, but the most significant is definitively outlining the link between genomics and biology. Most leading experts in the field hypothesize that proteomics will answer these questions.[9]

Additional proteomic research is vitally important to the progress of the coming biological revolution because proteins are the next step in the chain of biological life. Proteins form the structure and control the function of nearly every biological process including digestion, muscle contraction, each of the five senses, cognition, circulation and everything else. Figure 1 below depicts in a simplified approach the relationship between the genome and proteome.

Figure 1:[10]



The genome consists of many information packets called genes. These genes store genetic information in the form of DNA.

Genetic information stored in the genes is transcribed or copied from DNA molecules over to RNA. In the cell, ribosomes read RNA information in order to produce proteins.

The proteome is the entire collection of the body's proteins. Proteins actually do the body's "work." Proteins reveal the body's expressed genetic traits (i.e. eye color, blood type).

The Centre for Genetics Education specifically stated, "The next area where there will be rapid developments is called proteomics – the study of the gene products and how they work and interact with each other, the genes and other components in the cells."[11] As Cohen et al described above, researchers require much more knowledge and expertise regarding the vital, intermediate molecular tools (proteins) if science truly seeks to predict the natural biological course of life as well as the ability to alter the course of disease and enhance human performance.[12] The coming wave of proteomics research will yield that "Rosetta Stone."

Human Proteome Project. In September 2010, before 1200 scientists from 40 countries, the Human Proteome Organization announced the Human Proteome Project in Sydney, Australia at their Ninth Annual World Congress.[13] The organizers expect the research to take approximately 10 years and require $1 billion in funding. Just like the Human Genome Project, the results will be available to the public through open-source databases. According to the leaders of this effort, "The Human Proteome Project, by characterizing all 21,000 genes of the known genome, will generate the map of the protein based molecular architecture of the human body and become a resource to help elucidate biological and molecular function and advance diagnosis and treatment of diseases."[14] To help appreciate the size and magnitude of this research, Speicher recently offered his approximation, "[c]urrent estimates are that the human genome has about 50,000 genes…at least one million different protein components that are functionally distinct are likely to be produced by the human genome."[15]

In the early months of the Human Proteome Project, the scientific literature already contains evidence of notable successes. Researchers at the Institute for Systems Biology recently published the "gold standard" identification methodology for use by other protein researchers worldwide and it is already accessible to others via an on-line database. Although they studied laboratory specimens in a controlled laboratory setting outside, this methodology is an invaluable standardization methodology for other researchers in positively identifying proteins as they occur in their natural environment of the human body.[16] According to the principal investigator of this important study, "[w]e created technology that enables the identification of each protein encoded by the human proteome through targeted mass spectrometry."[17] The bulk of the remaining mapping effort for every human protein in its natural environment will rely on this technology, as such; this early finding is a critical enabler of subsequent efforts. Such important foundational

work so early in the Human Proteome Project's tenure serves a vital function in standardization and reproducibility of future research efforts. Additionally, early victories such as this build momentum and bolster funding, thereby increasing the likelihood of the overall project's sustained success.

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IMPLICATIONS FOR MILITARY MEDICINE

As it has for many centuries, management of trauma patients remains at the core of military medicine's rationale for existence. Despite US forces' technological superiority, serious injury and death persists as an unavoidable reality of war that is unlikely to disappear in the coming decades. While the civilian sector continually seeks improvement in all aspects of medical care, military medicine shoulders a unique responsibility to advance trauma care science given their vast experience in the field and continuing obligation to those in uniform as well as the American public at large.

Recent conflicts in Iraq and Afghanistan are the least deadly in American history thanks in part to advances in protective equipment and better medical care, particularly in the field of trauma medicine. In fact, these conflicts have the lowest death to wounded ratio of any conflict in recorded US history (dating back to WWI). Specifically, deaths comprise 12 percent of total casualties in Iraq and Afghanistan through 2009, one-half the rate seen for Vietnam and Korea, and one-third the rate seen in the two World Wars.[18] For military medicine to continue this record of improvement, trauma care must exploit advances in proteomic technology to discover new diagnosis and treatment modalities.

Trauma outcomes depend less on one's genetic make-up than most other human illness and diseases;[19] however, emerging research suggests proteomics could help solve the mysteries of trauma-induced physiological changes that frequently prove deadly. Following substantial trauma, poorly understood processes occur that induce massive inflammation, blood-clotting abnormalities and other syndromes. Increasingly thought to be protein-mediated, these processes often give rise to acute respiratory distress syndrome and multiple organ system failure, leading

causes of death among trauma patients. As an example, scientists at the University of Florida recently found evidence that proteins circulating in human cerebrospinal fluid could show utility as diagnostic or prognostic markers in patients suffering from Traumatic Brain Injury.[20] Additionally, researchers at the Pacific Northwest National Laboratory found significantly altered concentrations of 110 blood proteins among severe burn patients and approximately 50 of those proteins were not previously associated with burn response. As the Pacific Northwest team stated, these results "may reveal novel targets for therapeutic interventions as well as potential predictive biomarkers for patient outcomes such as multiple organ failure."[21]

One particularly useful application of proteomics in military medicine would be the development of therapeutic agents to extend the "golden hour." The "golden hour" is the first sixty minutes following trauma when the body is remarkably resilient and can remain alive in even the most dire cases until transport to definitive care at a medical facility. As stated previously, significant inflammation and other protein-mediated processes occur following trauma and their apex of life-threatening effects occurs after this "golden hour" window closes, often resulting in death. If unit-level medics could administer these medications to severely injured personnel effectively extending the "golden hour," they would save many lives on the battlefield. This is particularly true in places like Afghanistan where the tyranny of distance makes helicopter or ground evacuation to trauma centers within the "golden hour" extremely difficult.

Private sector pharmaceutical firms are unlikely to aggressively develop medications capable of these inflammation-delaying effects because the expiration of the "golden hour," and possibly the victim, is not a comparably significant problem for civilian healthcare. With civilian healthcare, the sixty-minute timeline is less problematic due to greater proximity of

hospitals and ambulance services. More importantly, there is no civilian equivalent of the unit medic, proximate to the injured individual in time and location, with these potentially life-saving medications in their possession. Due to these significant differences between civilian and military trauma care, particularly in austere and remote battlefield locations, the military services should take the lead in developing proteome-based agents capable of prolonging the "golden hour."

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IMPLICATIONS FOR MILITARY PERFORMANCE MODIFICATION

The trauma care implications discussed in the previous section are most likely to rely on agents targeted at physiological and protein-medicated processes occurring in all humans, not specifically developed or targeted towards the patient's unique proteome. The time to develop an agent specific to the victim simply does not exist in the early stages of a trauma situation. However, the same time constraints and development limitations do not exist for performance modification agents, thereby; an entirely new area of clinical research opens, offering a wide variety of military applications.

Proteomic technology will affect military operations in remarkable ways when it reaches maturity between 2030 and 2040. Knowledge from the Human Proteome Project will enable development of highly targeted and personalized modification, particularly with regard to performance enhancement. Simultaneously and at the opposite end of the effect spectrum, the path to degrade the performance of others through precision attack also reveals itself.

Performance Enhancement. Current pharmaceutical performance enhancement agents such as "go" and "no-go" pills (modafanil, dextroamphetmine, zolpidem, etc.) do not exhibit sufficient specificity for more widespread use than seen today. While these agents effectively prolong wakefulness, they have variable results between different individuals making it difficult to use them more broadly for sustained, long-duration air operations and with certain special operations forces. Furthermore, because current agents bind to receptors in the human body in a relatively non-specific manner (at least compared to agents developed in the proteome era), side effects often limit the use of these agents for extended durations and in higher doses. Until new

modalities emerge, pharmaceutically mediated performance enhancement will remain limited in duration and mission type.

In the future, knowing an operator's or senior leader's specific proteome allows the design of pharmaceuticals specifically designed for the individual. While the agents developed for one specific operator or senior leader may produce the desired effect in an effective and repeatable manner, the very same agent may cause completely different effects or even toxicity in other humans. Additionally, because these agents will be so much more specific to the desired receptor's protein binding sites, side effects will be minimal or non-existent, thus, no longer serving as the primary rate-limiter in higher dose or longer duration use. Such agents may enable certain future military members to break free from typical circadian-rhythm-based, sleep-wake cycles, allowing more frequent employment of 36-48 hour continuous missions and shorter, but more restorative, crew rest periods.

Performance Degradation. The same proteome-based development process that enables development of performance enhancement agents also opens the door for innovation of highly targeted performance degradation agents for those nations, groups or individuals who choose to purse this research.

When used in an attack capacity, agents developed using an individual's specific proteomic make-up will no longer possess the dangers of current chemical and biological weapons. The collateral damage caused by current weapons of mass destruction, particularly the rapid and poorly controllable transmission of biological agents, makes their use anathema given the current state of technology. Only the most rogue regimes currently embrace these weapons and are likely to use them. At this point, it is not clear if existing weapons of mass destruction

treaties address proteomic technology. If not restrained through revised treaties, it is reasonable to expect mitigation of current limitations on the use of technology targeting a specific individual's genetic and proteomic makeup. Furthermore, if the performance degradation agent is rendered non-transmissible to others and potentially less-than-lethal to the desired target (as in the introductory scenario), one could reasonably expect the use of these agents to increase. In aggregate, this emerging technology may usher in an entirely new approach to deterrence.

Development of targeted performance degradation agents with military utility will certainly remain controversial and many nations may decline to pursue these capabilities based on either ethical or social constraints. Conversely, some nations may argue these weapons are even more humane than conventional weapons so commonly used today. Certainly, some nations will adopt this view and make these agents an important part of their overall arsenal. If only because the technology exists for fielding these agents, almost assuredly, at least small numbers of nations, groups or individuals will remain undeterred in their pursuit to acquire these agents. As such, the US must remain at the cutting edge of this technology, not only to understand the possible threats faced globally, but also to understand potential avenues for countermeasure development.

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PROTEOME RESEARCH BY PEER COMPETITOR NATIONS

Research into the complexities of the human proteome occurs not only in the US, but in many other advanced nations around the world. Primarily seen as medical research and a path to development of better medications, the majority of research occurs at either pharmaceutical firms or other public research centers. Some of these entities are state sponsored and others are university affiliated, but advances in medical science appear to be the primary driver for the majority of this work. Nations who lead innovation will realize significant health benefits for their citizens and notable economic strength in the ever-growing healthcare marketplace. In addition, they may also have the means to possess a potentially powerful military weapon.

The Human Proteome Organization is the international body managing the Human Proteome Project and their membership includes scientists from around the world.[22] In the first months of the initiative, the US, Japan, Russia and China continue their strong scientific tradition and highlight the list of several dozen nations actively involved in this monumental undertaking. Each nation or large organization is "adopting" at least one of the 23 human chromosomes (the Russian's have claimed Chromosome 18) [23] and subsequently identifying each of its associated proteins.

Most impressive at this early stage of the Human Proteome Project is China, as evidenced by their establishment of a generous funding stream. The lead Chinese proteome research organizations have already secured 30 million dollars per year in funding and expect it to double in the next few years. Furthermore, the central government recently announced a 180 million dollar cash infusion.[24] These are very large sums of money in the realm of basic laboratory science and may well place China ahead of other advanced scientific nations. In fact, a Human

Proteome Organization board member described this level of investment as "impressive and unprecedented."[25]

In addition to a solid financial foundation, Chinese researchers are also assembling a robust research partnership and strategic plan to achieve their goals. In terms of organization, a formal proteome research partnership now exists between powerhouses Peking University and the Chinese Academy of Sciences, along with several other institutions.[26] This organizational structure centralizes and prioritizes effort among partner entities, facilitates allocation of resources and ensures information transfer. The US and other scientific leading nations must accelerate and strengthen their proteomic research efforts to match the early example set by China.

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CONCLUSION

Humanity is at the brink of a biological revolution. The next several decades will unveil an unprecedented rate of technological advance, particularly in the fields of genomics and proteomics. While understanding the genome is the essential first step towards this revolution, the real development and exploitation of this technology will happen via proteomics.

The Human Proteome Project is the critical bridge between knowledge of the genome and full operationalization of tactics and techniques to exploit biological processes in very deliberate and specific ways. When these linkages are established, revolutionary advances in understanding of human life will influence nearly every aspect of society. As with most new technologies, there will dual uses. Humans will benefit mostly from the application of proteomic knowledge in the medical field, but the military will also change dramatically. Through either better battlefield trauma care or targeted performance modification, these future modalities will surely find their way into the bloodstreams of American uniformed personnel, whether it is voluntary, or from an adversary's attack. Either way, the Air Force must understand and master this technology as it unfolds if it is to continue to accomplish its mission.

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